THE EFFECTS OF VARIOUS ANTISPASMODIC DRUGS ON THE PRESSURE AND ACTIVITY OF THE DISTENDED COLON IN DOGS AND MAN

BY

JUSTIN BERNARD HOEKSTRA

A. B., Calvin College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PHYSIOLOGY
IN THE GRADUATE SCHOOL OF THE
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Introduction

In recent years a number of different drugs known as antispasmodics have been prepared to take the place of atropine and papaverine in relieving spastic conditions of the gastro-intestinal tract with the purpose of obtaining an active compound which has no undesirable side effects. The following factors should be considered when the effects of these drugs are observed on intact animals: (1) the kind of animal used, (2) the part of the gastro-intestinal tract to be studied, (3) the degree of muscular tone present at the time of the experiment, (4) the degree of segmenting or peristaltic activity present at the time of the experiment, and (5) the presence or absence of anesthetics at the time of the experiment.

Many different methods have been used to record the motor activity of the gastro-intestinal tract. Templeton and Lawson (1931) used a balloon recording system and found that colonic activity was periodic in nature. They also described three types of contractions in the colon. Atkinson, Adler, and Ivy (1943) report similar results for the human colon using the same method.

Experimental

Part I

A method of recording colonic activity was developed which is believed to be the most physiological and least abnormal method employed up to this time. It consists of introducing a given volume of gas into the colon of dogs and man and recording the pressure changes in the lumen by

means of a water manometer. This gas was retained in dogs by cementing a rubber sheet to the skin around the anus with rubber cement. This formed an air tight system and permitted pressure changes to be recorded by means of an open-tipped catheter which passed through the center of the rubber sheet into the lumen of the colon. The water manometer was equipped with a glass float which recorded the pressure changes on a smoked kymograph drum.

Dog's colons were also injected with Thorotrast during a sterile operation and after recovery roentgenograms could be taken to show the state of activity and distention or tone present in the organ.

Part II

The physiological response of the colon to the introduction of gas was studied under several different conditions. The activity of the colon was observed in unanesthetized dogs for as long as two hours following the introduction of a volume of gas into the lumen sufficient to produce satisfactory activity. The volume of gas required for this response varied from fifty to two hundred cubic centimeters depending largely on the size of the dog. The same procedure was repeated in dogs under total Nembutal anesthesia. Simultaneous measurements of pressure in two different regions of the descending colon were also made. This was accomplished by introducing two open-tipped catheters into the lumen of the colon by way of rectum. The effects of pure oxygen, nitrogen, carbon dioxide and air on colonic activity was also studied both by the graphic and roentgenogram methods. Finally, the effects of progressive distention of the dog's colon with air was studied.

The results of these experiments show that the activity of the colon varies from dog to dog and from experiment to experiment on the same dog. The average of 224 experiments on unanesthetized dogs shows that there are 18.13 contractions of the colon in a fifteen minute period, each

contraction having an average duration of 0.8 minutes. The basal or tonal pressure is 7.34 centimeters of water and the amplitude of contraction is 6.16 centimeters of water. The volume of the gas in the colon decreases very slowly with time. Under Nembutal anesthesia the number of contractions decrease, the individual contractions have a greater duration, the tonal pressure is lower and the amplitude of contraction is greater than in the unanesthetized dog. The activity is continuous in both anesthetized and unanesthetized dogs for at least two hours. Pressure changes occur simultaneously along the lumen of the descending colon. Carbon dioxide is rapidly absorbed and decreases tone and activity of the colon while air, nitrogen and oxygen show little change in volume and provide a good stimulus for activity. The colon responds to the continuous introduction of air by a gradual increase in the amplitude of contractions, tone and size of the lumen. At a pressure of 8.32 centimeters of water, however, the colon can no longer adjust to an increase in volume and pressure rises sharply. Under Nembutal anesthesia the colon is able to tolerate much less air and responds by contracting spasmodically in an effort to expel the gas.

Part III

The effects of seven different antispasmodic drugs were studied on the colon of dogs and man. In the experiments performed on dogs the drugs were injected intracardially while in the case of man the drugs were administered orally. Atropine was given to dogs at a dosage of 0.02 mg./kg. of body weight while papaverine, Syntropan, Trasentine, Amethone and Profenil were given at a disage of 2.0 mg./kg. In the experiments on man, Syntropan, Trasentine, Amethone and Pavatrine were given at the recommended therapeutic dosage.

In order to determine whether the drugs were producing a real effect on the colon, control experiments were performed

where activity was followed for the same length of time as in the drug experiments. A small amount of Nembutal (2.5 mg./kg.) was injected in some experiments both alone and along with the antispasmodic drugs. The effect of the drugs was also studied under total Nembutal anesthesia.

The results of these experiments show that atropine and papaverine are the most active antispasmodic drugs on the colon of unanesthetized dogs. The addition of a small amount of Nembutal to the dose of the drugs increases their inhibitory activity in most cases and can be considered to be a synergistic action with Amethone, papaverine and Syntropan particularly with respect to the lowering of tone. All the drugs except papaverine showed very good depression under anesthesia contrasted to their slight effect in the unanesthetized dog. In man Syntropan and Trasentine showed no activity while Pavatrine and especially Amethone were fairly active. The addition of 25 mg. of Nembutal markedly increased the effect of Pavatrine.

Summary

The introduction of air into the colon produces continuous activity for at least two hours, and there is a definite limit to which the colon can be distended. Nembutal anesthesia markedly changes the pattern of colonic activity in dogs. The synthetic antispasmodic drugs are relatively ineffective in the unanesthetized dogs and man but have a much greater activity in the Nembutal anesthetized dog. In some instances there is a significant synergism between the drugs and a small dose of Nembutal.

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VITA

The author was born on July 1, 1922, in Grand Rapids, Michigan. He attended the Oakdale Christian School and the Grand Rapids Christian High School from which he graduated in June, 1939. He matriculated at Calvin College in September, 1939, and was awarded the Bachelor of Arts degree in June, 1943, with a major in Chemistry. He entered the Graduate School of the University of Illinois in October, 1943, and was awarded an Abbott Research Fellowship in Physiology for three successive years. He served as a teaching assistant in Physiology during the summer semesters of 1945 and 1946. He was appointed a Fellow in Physiology by the University of Illinois for the school year 1946 to 1947.

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